WEGENER'S GRANULOMATOSIS: CASE REPORT AND REVIEW OF THE LITERATURE

WILLIAM F. ROBBETT, M.D.
Chairman

JOHN S. RUBIN, M.D.
Senior Resident

Department of Otolaryngology
Manhattan Eye, Ear and Throat Hospital
New York, New York

WEGENER'S granulomatosis, although very uncommon, is perhaps the form of vasculitis most frequently recognized in general otolaryngology practice. As an entity its clinical and pathologic similarity to several other disorders creates difficulty in establishing a diagnosis. Early diagnosis is extremely important because it predicates therapy.

CASE HISTORY

This 68-year-old white man presented with a one-year history of nasal crusting and left-sided epistaxis, worsening during the two months prior to admission. A 15-pound weight loss occurred during this time. Progressive hearing loss had been noted during the six months prior to admission, as was a change in shape of the external nose and decrease in the visual acuity of the left eye. A one-month history of dyspnea on moderate exertion was elicited. The past history is significant for a tachycardia of one-year duration, unsuccessfully treated with digoxin. There was no history of hemoptysis, hematemesis, or chest pain.

Physical examination revealed a cachectic appearing man in no acute distress. Blood pressure was 150/90 mm.Hg, pulse 120 and regular, respirations 20/min. Examination of the left eye revealed ptosis of the upper lid, decreased extraocular movements, and decreased visual acuity. Saddle deformity of the nasal dorsum and deflection of the caudal septum to the right were noted. Examination of the vestibules revealed friable granular tissue, crusting, and atrophic mucosa over the turbinate bones on the left side

*Presented before the Section on Otolaryngology of the New York Academy of Medicine December 19, 1979.

Address for reprint requests: William F. Robbett, M.D. Manhattan Eye, Ear and Throat Hospital, 210 East 64th Street, New York, N.Y. 10021.

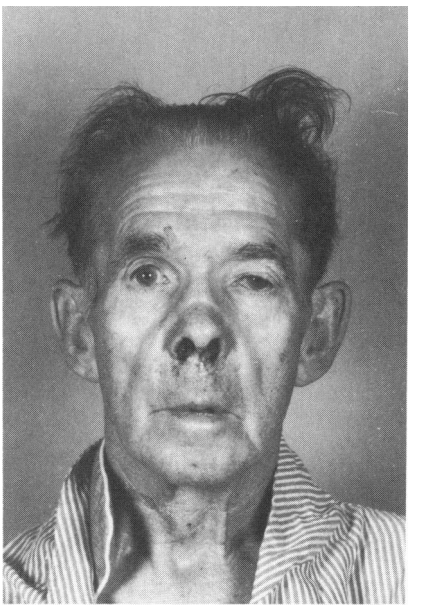

Fig. 1. Ptosis of the left upper eyelid. Saddle nose deformity and granular tissue in both nasal chambers are evident.

(Figure 1). The nasopharynx was unremarkable except for clots extending from the nose. Both tympanic membranes were discolored, consistent with serous otitis media.

The larynx and neck were unremarkable. Lungs: scattered rhonchi and wheezes to auscultation. Heart: tachycardia without murmurs, heaves, thrills, or rubs. Abdomen: no palpable abnormalities. Extremities: 3+ pulses with fine tremor in the extended fingers. No focal neurological deficits other than the described left ocular findings.

Laboratory examinations: Leukocyte count 15,000 cmm. with a left shift. Hemoglobin 12.8 g./dl., hematocrit 36 vols. %, sedimentation rate 123/hour. Clotting profile was normal. Urinalysis revealed 2-3 leukocytes/HPF. Blood urea nitrogen 28. Creatinine 1.5 mg./dl. Liver enzymes normal. VDRL nonreactive. Electrocardiogram: sinus tachycardia. Chest roentgenogram multiple nodular densities in both lung fields, apical pleural changes consistent with old granulomatous disease, and a cavity lesion in the right lower lung field. Tomographic examination of the paranasal sinuses revealed a soft tissue mass in the left antrum with increased thickness of the mucoperiosteal membrane and increased soft tissue in the upper half of both nasal cavities. Clouding of the frontal, sphenoid, and ethmoid

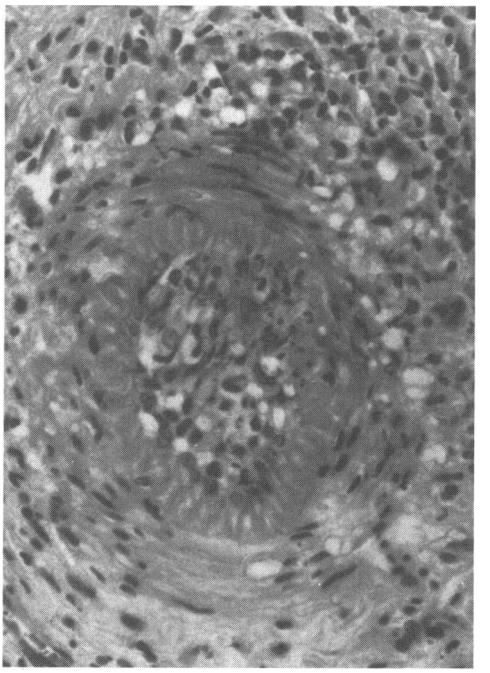

Fig. 2. High power micrograph from nasal biopsy revealing vasculitis with vascular occlusion. High power (40X) hematoxylin and eosin.

sinuses was readily apparent. Bony destruction of the left ethmomaxillary septum was noted. The left inferior and middle turbinates were not identifiable on the roentgenograms.

Audiogram revealed a bilateral 30 dB conductive hearing loss consistent with serous otitis media. Ophthalmologic consultation was requested and recorded as: right visual acuity 20/40, left visual acuity 20/200. Ptosis of 3 mm. of the left upper lid. Left extraocular motions were limited except for abduction. Those on the right were normal. Fundoscopic examination was within normal limits.

Hospital course: The patient was given propranolol with subsequent resolution of the tachycardia. Using the operating microscope, both tympanic membranes were opened and fluid aspirated from the middle ears. Polyethylene ventilation tubes were inserted into the tympanic membrane incisions to relieve the hearing loss. A nasal biopsy was performed (Figures 2 and 3).

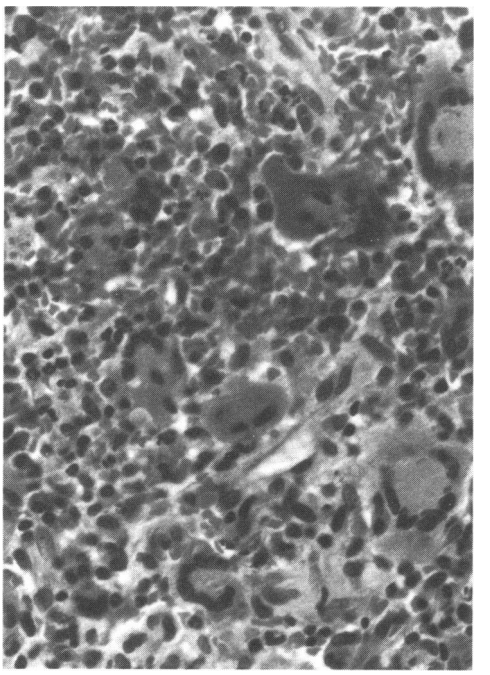

Fig. 3. Photomicrograph from nasal biopsy revealing chronic inflammation and giant cells. High power (40X) hematoxylin and eosin.

Histologic examination of the excised nasal tissue was reported as chronic inflammatory tissue of both nasal cavities with vasculitis, vascular occlusion, and foreign body giant cells consistent with Wegener's granulomatosis.

Clinically, the patient had progressive loss of vision in the left eye. He became so weak that he could not get out of bed. His appetite decreased and weight loss was more obvious. The patient was then given 60 mg. of prednisone daily in divided doses. Clinical response to the prednisone was remarkable. The patient began to eat without urging and soon was walking to the bathroom and in the hospital corridor. Vision in the left eye began to return and ptosis of the left lid decreased. He was then discharged from the hospital with the treatment plan of Cytoxan 50 mgm. twice a day and prednisone 10 mgm. three times a day.

The patient continued to improve with this course of therapy. The sedimentation rate decreased from 123 to 84/hour. The left eye symptoms

completely disappeared. Vision returned to normal and there was no evidence of the left lid ptosis or proptosis of the left eye. Appetite improved and a gradual weight gain was noted. A chest roentgenogram showed total recession of the nodular densities. The appearance of the interior of the nose improved remarkably, without evidence of granular tissues, crusting, or bleeding.

Several weeks later the patient said he felt much improved except that he had greater exertional dyspnea. An electrocardiogram showed no changes from previous studies. A few days later the patient died at night in his sleep. Postmortem examination could not be obtained. It was speculated by all physicians involved in his care that the cause of death had a cardiac basis.

Wegener's granulomatosis is a necrotizing granulomatous vasculitis which occurs in a localized form affecting the upper and lower respiratory tracts and a disseminated form with renal involvement. The male-to-female ratio is 3:2; the peak incidence is during the fourth and fifth decades of life. The etiology is unknown. A hypersensitivity mechanism has been suggested, but no antigen has yet been isolated. Head and neck symptoms are the initial complaint of 90% of the patients.

The most common symptoms are severe rhinorrhea and nasal crusting—the rhinorrhea being clear, purulent, or blood tinged. Clinically, the turbinates and septum appear granular. As the disease progresses, scarring causes vestibular stenosis, and ischemic changes lead to progressive loss of soft tissue support with saddle nose deformity. A septal perforation frequently occurs.[2,6,8] Involvement of the paranasal sinuses is present in more than 90% of the patients and may be quite extensive. The disease is usually first seen in the maxillary and ethmoid sinuses. Secondary bacterial sinus infections are common, and the pathogen most commonly cultured is *Staphylococcus aureus*.[2] Other head and neck symptoms of Wegener's granulomatosis include otologic involvement. Seen in 40% of patients, it usually appears as a conductive hearing loss caused by obstructive granulations, either of the nasopharynx or of the middle ear mucosa. This leads to serous otitis media.

Complaints referrable to the oral cavity include persistent sore throats and ulceration of the palate. Mucositis with hyperkeratosis preceeds the ulceration. 25% of the patients have laryngotracheal airway involvement consisting of superficially ulcerating mucositis with gradual constriction, most often involving the subglottic area. Orbital changes, consisting of

granulomatous involvement of the sclera, conjunctiva, and cornea, occur in 40%.

Pulmonary symptoms consist of cough, hemoptysis, and pleuritic pain. Frequently, however, symptoms referrable to the pulmonary disease are minimal. It may be completely silent.[4] Renal involvement occurs in 80-85% of patients and is said always to be present in the generalized form of the disease, characterized by proteinuria, hematuria, and red cell casts. The renal disease may progress rapidly to failure, leading to death. Unlike polyarteritis nodosa, hypertension associated with renal disease is uncommon.[10] Cardiac involvement may also be rapidly fatal because of pericarditis, myocardial necrosis, and arrhythmias caused by coronary vasculitis.

Other organ-system involvement includes a transient polyarthritis in 50%; mononeuritis, usually secondary to vasculitis, in 20% (much like that in polyarteritis nodosa); necrotizing angiitis with thrombosis of dermal vessels yielding skin ulcerations and alopecia in 40% of the patients so afflicted.[8]

In attempting to make the early diagnosis of Wegener's granulomatosis, most laboratory values may be within normal limits. Possible abnormal values include the hematologic profile, which usually has mild leukocytosis and normochromic anemia. Urinalysis may show microhematuria and proteinuria, and biochemical studies may include elevated serum blood urea nitrogen and creatinine. Sedimentation rate is extremely important, and frequently is more than 80 mm./hr. Reflecting the hyperimmune theory of etiology, the C3 and C4 complement levels may be elevated with a hyperglobulinemia consisting of elevated IgG and IgA. Antinuclear antibodies and systemic lupus erythematosus preparations are normal. Rheumatoid factor is often elevated.[7]

Radiologic findings may include abnormal sinus radiographs and, although not diagnostic of the disease, they help to delineate the extent of the disease. Early findings resemble inflammation but later in the disease the bone destruction resembles neoplasm. Laryngeal roentgenograms may reveal subglottic narrowing. Chest roentgenograms are also nondiagnostic, showing either patchy fluffy infiltrates or nodular densities. Commonly, lesions are bilateral. Cavitation is frequent, and air-fluid levels may be visible. Thin walled cavities similar to those seen in coccidiomycosis can occur. Any area of the lung may be affected, and the infiltrate may be fleeting.[10,12]

Definitive diagnosis is made by biopsy. Microscopically, the disease is

identified by necrotizing granulomatous lesions with extensive ulcerations spreading deeply into surrounding tissue. Independent focal necrotizing vasculitis involving both arterioles and venules is the other outstanding microscopic finding. Renal biopsies are considered important to define the extent of the disease. Biopsy most frequently shows focal necrotizing glomerulonephritis with crescent formation and destruction of one or more glomerular capillary loops. Immunofluorescent staining reveals a coarse granular pattern.[9]

Wegener's granulomatosis must be differentiated from many other diseases to institute proper treatment. These can be broken down into the vasculitic diseases such as polyarteritis nodosa, systemic lupus erythematosus, scleroderma, and dermatomyositis; neoplastic diseases such as lymphoma, Hodgkin's disease, or midline malignant reticulosis; and such granulomatous diseases as tuberculosis, sarcoidosis, and syphilis.[8,9,12]

The diagnosis can often be made with a biopsy or with specialized testing. Until recent years, Wegener's granulomatosis and midline malignant reticulosis were considered different stages of the same disease. It is particularly important to differentiate between these two entities. Midline malignant reticulosis (also named polymorphic reticulosis and lethal midline granuloma) is a malignant neoplasm of lymphoreticular cells characterized histologically by an infiltrate of malignant cells admixed with normal inflammatory cells. Clinically, its presentation is similar to Wegener's granulomatosis. Patients frequently complain of nasal crusting and granulations. However, the treatment of midline malignant reticulosis is specifically with radiation and has a good prognosis for cure. Wegener's granulomatosis should never be treated with radiation therapy.

The prognosis has improved in Wegener's granulomatosis with recent therapeutic advances. Formerly, the disease was rapidly fatal, the mean survival time being five months.[11] With the advent of chemotherapy cures can now be achieved. At present cyclophosphamide (Cytoxan) is the drug of choice (1-2 mg./kg./day) with azathioprine (Imuran) as a satisfactory substitute. Steroids, previously the primary medication, are used now only to decrease inflammation. Antibiotics are often useful in the treatment of secondary infection.

Treatment is stopped one year after all traces of disease have disappeared or if toxicity ensues. To measure clinical response to therapy, such parameters as decreased respiratory symptoms, remission of peripheral manifestations of vasculitis, and arrest of renal deterioration are useful.[2]

REFERENCES

1. DeRemee, R. A., McDonald, T. J., Harrison, E. G., and Coles, D. T.: Wegener's granulomatosis, anatomic correlates, A proposed classification. *Mayo Clinic Proc. 51:*777-81, 1976.
2. Fauci, A. S. and Wolff, S. M.: Wegener's granulomatosis: Studies in eighteen patients and a review of the literature. *Medicine* (Baltimore). *52:*535-58, 1973.
3. Fechner, R. E. and Lamppin, D. W.: Midline malignant reticulosis: A clinicopathologic entity. *Arch. Otolaryngol. 95:* 467-76, 1972.
4. Israel, H. L., Patchefsky, A. S., and Saldana, M. J.: Wegener's granulomatosis, lymphomatoid granulomatosis, and benign lymphocytic angiitis and granulomatosis of the lung: recognition and treatment. *Ann. Intern. Med. 87:*691-99. 1977.
5. Kornblut, A. D., Gadek, J. E., Fauci, A. S., and Wolff, S. M.: Head and neck manifestations of histiocytic medullary reticulosis. *Laryngoscope 88:*1596-1602. 1978.
6. McDonald, T. J., DeRemee, R. A., Kern, E. B., and Harrison, E. G.: Nasal manifestations of Wegener's granulomatosis. *Laryngoscope 84:*2101-11. 1974.
7. Schlechter, S. L., Bole, G. G., and Walker, S. E.: Midline granuloma and Wegener's granulomatosis: Clinical and therapeutic considerations. *J. Rheumatol. 3:*241-50. 1976.
8. Schramm, V. L., Myers, E. N., and Rogerson, D. R.: The masquerade of vasculitis: Head and neck diagnosis and management. *Laryngoscope 88:*1922-34. 1978.
9. Scully, R. E., Galdabini, J. J., and McNeely, B. U.: Case records of the Massachusetts General Hospital. Case 19-1976. *N. Engl. J. Med. 294:*1052-56, 1976.
10. Case records of the Massachusetts General Hospital, Case 47-1977. *N. Engl. J. Med. 297:*1164-72. 1977.
11. Walton, E. W.: Giant cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br. Med. J. 2:*265-70, 1958.
12. Wolff, S. M., Fauci, A. S., Horn, R. G., and Dale, D. C.: Wegener's granulomatosis. *Ann. Intern. Med. 81:*513-24. 1974.